REMARKS

This Amendment, filed in reply to the Office Action dated June 12, 2009, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1-4, 6, 13 and 15-16 are all the claims pending in the application. Claims 5, 7-12 and 14 are canceled. Claims 1-11, 13 and 14 are rejected. Claims 1 and 13 are amended herewith. Claims 15 and 16 are newly added. Exemplary support for the amendment to Claims 1, 13 and 15-16 can be found throughout the specification, at for example page 2, lines 1-29 and page 124, line 1 to page 126, line 10. New Claims 15 and 16 are further supported by original Claims 8 and 9, which are herewith canceled. Applicants request examination of new Claims 15 and 16 as Claim 1, directed to a thiazole derivative, is now in condition for allowance and Claim 15 and 16 are directed to the use of the thiazole derivative and contains all of the limitation of the now allowable Claim 1.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Objection to Specification

On page 7 of the Office Action, the Examiner states that there is no brief description of the figure and other required subheadings in the specification. In response, Applicant herewith amends the specification to add the header and a brief description of the drawing. Support for the amendment may be found throughout the specification, at for example Figure 1 and at page 125, lines 6-20.

Withdrawal of the objection is respectfully requested.

Claim Objection

On page 7 of the Office Action, the Examiner objects to Claims 1-11 as claiming a non-elected invention. In response, Applicant herewith amends Claim 1 to a thiazole derivative that recites, *inter alia*, "wherein X^1 and X^2 are different from each other and represent a sulfur atom or a carbon atom" and R^1 is "selected from the group consisting of benzothiazolyl, benzoxazolyl, and benzo(1,3)dioxolyl." The amendment is directed to the elected invention on April 30, 2009, wherein Applicant elected Group II, directed toward Claims 1-6, drawn to compounds of formula 1, where "one of X^1 and X^2 is S, the other is C, and R^1 is condensed phenyl selected from benzothiazolyl, benzoxazolyl, and benzo(1,3)dioxolyl."

Withdrawal of the objection is respectfully requested.

RESPONSES TO REJECTIONS

A. Rejection under 35 U.S.C. § 112, first paragraph

A. Claims 7-11 are under 35 U.S.C. § 112, first paragraph, as lacking enablement for the following reasons:

(1) Claims 10-11 allegedly fail to recite the compounds critical or essential to the practice of the invention and the Office Action further states that the scope of the claims are broader than the enabling disclosure of the specification.

(2) The specification is allegedly not commensurate in scope with the scope of Claims 7-11. The Office Action refers to the factors in *In re Wands*, stating *inter alia*, that the breadth of the claims encompasses many compounds with different substituents and treating various diseases arising from the inhibition of ALK5, not all of which are known today. Furthermore, the Office Action asserts that Claims 7, 9-11 are attempts by Applicant to claim

treatment of diseases known and yet to be discovered arising from inhibition of ALK5. They are reach-through claims and are no longer patentable under the US patent practice.

(3) The Office Action asserts that not every compound capable of inhibiting ALK5 is applicable for treating the diseases listed in claim 8. The Office Action states that the specification lists diseases for which the instant compounds are applicable, but states that they are "deemed speculations because there is no conclusive evidence that the compounds would work as claimed." The Office Action further states that the only assays disclosed in the specification are inhibition of Smad2/3 phosphorylation and hair follicle proliferation and that "[w]hile IC_{50} values for Smad2/3 inhibition are disclosed for a few examples of the compounds, no results are disclosed for the proliferation test and no explanation how the IC_{50} values correlate with each disease." See page 5 of the Office Action.

Claims 7-11 have been cancelled without prejudice or disclaimer, therefore the rejection against these claims are moot.

Applicants respectfully submit that new Claims 15 and 16 also comply with the requirements of 35 U.S.C. § 112, first paragraph. New Claim 15 is directed to a method of treating glomerulonephritis, diabetic nephropathy, hepatic fibrosis, liver cirrhosis, pulmonary fibrosis, or alopeciarosis in a subject, the method comprising administering to the subject a composition comprising a therapeutically effective amount of the thiazole derivative or a pharmaceutically acceptable salt thereof according to claim 1.

Initially, Applicant notes that "[d]etailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention." M.P.E.P. §2164. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable

correlation to the entire scope of the claim...[and] one skilled in the art based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. M.P.E.P. §§2164.01(b) and (c). Also, "[c]ompliance with the enablement requirement of 35 U.S.C 112, first paragraph, does not turn on whether an example is disclosed." M.P.E.P. §2164.02.

The specification provides sufficient guidance such that one of ordinary skill in the art would understand how to use the claimed thiazole derivative, an ALK5 inhibitor, to treat the above listed diseases. In this regard, the specification provides a thorough discussion of the state of the art, e.g., as discussed at pages 1-4 of the present specification. Page 1 of the specification teaches that the claimed compound has an inhibitory action on activin receptor like kinase 5 (ALK5), which is a type of TGF-β type I receptor. The specification further teaches that one of ordinary skill in the art would understand that an inhibitor of ALK5 suppresses the accumulation of extracellular matrix induced by TGF-β by way of blocking TGF-β /Smad signals. See page 1, line 20 to page 2, line 3. Indeed, TGF-β has been shown to be deeply involved in fibrosis or glomerulonephritis in renal disease such as glomerulonephritis or diabetic nephropathy. See page 2, lines 5-10 and page 2, lines 21-29.

One of ordinary skill in the art would understand that ALK5 inhibitors, such as the claimed compound, are useful as pharmaceutical products for treatment or prevention of various diseases associated with fibrosis of kidney, liver or lung, etc. See page 2, lines 21-29. The use of ALK5 inhibitors or anti-TGF-β antibodies as treating various diseases has been widely reported

in the art.[1] For instance, Peterson, M. et al.,[2] discloses that the compound GW788388, a TGF-beta type I receptor inhibitor reduced renal fibrosis and decreased the mRNA levels of key mediators of extracellular matrix deposition in kidneys. The study described by Peterson et al. shows that the inhibitor is a potent and selective inhibitor of TGF-beta signaling *in vitro* and renal fibrosis *in vivo*. Furthermore, Gellibert F. et al., [3] discloses that GW788388, significantly reduced the expression of collagen Ia1 mRNA when administered orally in a model of puromycin aminonucleoside-induced renal fibrosis. Moon et al.[4] and Grygielko et al.[5] respectively disclose that IN-1130 and SB-525334, a ALK5 inhibitor, suppress fibrogenic process, and is useful for the treatment of renal fibrosis and produces statistically significant reductions in renal PAI-1 mRNA. As a further example of the various pharmaceutical uses of ALK5 inhibitors, de Gouville et al[6]., discloses that GW6604, increased liver regeneration in TGF-beta overexpressing mice and concludes that inhibition of ALK5 could be a new approach

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[1] In accordance with M.P.E.P. § 609.05(c), the documents cited herein in support of Applicants' remarks are being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08A & B is believed to be necessary.

[2] Peterson, M. et al., Oral Administration of GW788388, an inhibitor of TGF-beta type I and II receptor kinases, decreases renal fibrosis, Kidney Int., V. 73(6), 705-15 (March 2008)

[3] Gellibert, F. et al., Discovery of GW788388: a potent, selective, and orally active transforming growth factor-beta type I receptor, Dept. of Medicinal Chemistry and Biology (abstract attached)

[4] Moon, JA et al., IN-1130, a novel transforming growth factor-beta type I receptor kinase (ALK5) inhibitor, suppresses renal fibrosis in obstructive nephropathy, Kidney Int. v. 70(7): 1234-43 (October 2006)(abstract attached).

[5] Grygielko ET, et al., Inhibition of gene markers of fibrosis with a novel inhibitor of transforming growth-factor beta type I receptor kinase in puromycine-induced nephritis, J. Pharmacol Exp. Ther. V. 313(3): 943-51 (June 2005)(discussed in Applicant's specification at page 2, line 24).

[6] de Gouville AC, Inhibition of TGF-beta signaling by an ALK5 inhibitor protects rats from dimethylnitrosamine-induced liver fibrosis, Br. J. Pharmacol, v. 145(2):166-77 (May 2005).

to treat liver fibrotic diseases by preventing matrix deposition and promoting hepatocyte regeneration. Higashiyama et al.[7] reports that ALK5 inhibition attenuated the tissue fibrosis including pulmonary fibrosis, renal fibrosis and liver fibrosis. Ziyadeh et al.,[8] teaches that when a neutralizing anti-TGF-β antibody was administered to a Type 2 diabetes model mouse, the expansion of mesangium matrix was decreased, the creatine clearance was corrected and the progress of renal failure in diabetic was able to be obstructed. Foitzik K et al.[9], reports that when TGF-β1 is injected in mouse skin, apoptosis of hair follicle is induced and Foitzik suggests that TGF-β signal would increase hair follicle in anagen, which would lead to the improvement of the condition of alopecia. Kasuga et al.[10], reports that a control of the TGF-β receptor using a human antibody resulted in decrease of α-smooth muscle actin expression and a decrease of deposition of extracellular matrix suppression and was expected to lead to improvement of the condition of nephritis. Finally, Bonniaud et al.[11] discloses that an ALK5 inhibitor inhibits the induction of fibrosis and blocks progressive fibrosis when administered transiently to animals with established fibrosis. Thus, reference to these teachings, in addition to Applicants' disclosure as discussed above, clearly indicates that sufficient guidance is provided for treatment of the diseases encompassed by the claim 15 by an ALK5 inhibitor, such as the claimed compound.

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[7] Higashiyama, et al., Inhibition of active receptor-like kinase 5 attenuates bleomycine-induced pulmonary fibrosis, Exp. Mol Pathol., v. 83(1):39-46 (August 2007).

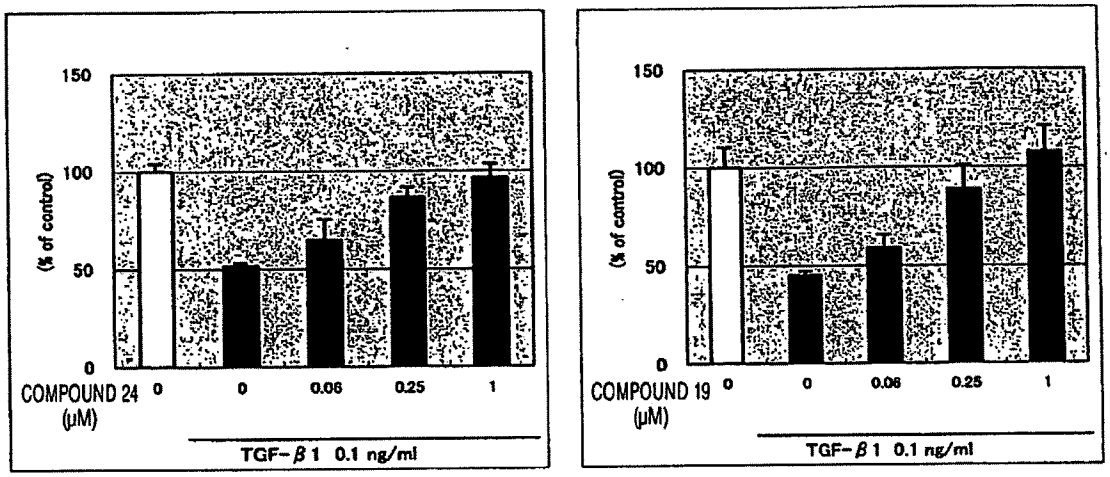
[8] Ziyadeh et al., Proc. Natl Acad Sci USA, v. 97(14): 8015-8020 (2000).

[9] Foitzik K et al., FASEB J. v. 14: 752-760 (2000)(discussed in Applicants specification at page 3, line 11).

[10] Kasuga et al., Kidney Int, v. 60(5):1745-1755 (2001).

[11] Bonniaud P., et al. Progressive transforming growth factor beta 1-induced lung fibrosis is blocked by an orally active ALK5 kinase inhibitor, Am J. Respir Crit Care Med., v. 171(8):889-98 (April 2005).

Further, based upon the nature of ALK5 inhibitor, which is to suppress the accumulation of extracellular matrix induced by TGF-β by way of blocking TGF-β /Smad signals, the present specification demonstrates that the claimed compound is useful for treatment of various diseases associated with fibrosis of kidney, liver or lung, etc. Example 1 discloses an Smad2/3 phosphorylation inhibitory test wherein the inhibitory activities of the compound of the present invention against Smad2/3 phosphoryolation caused by TGF-β1 stimulation were measured, and IC_{50} values were calculated. The results of Example 1 are shown in Table 2. Furthermore, Example 2 discloses a hair proliferation test and shows the numbers of living cells when TGF-β1 was solely administered thereto and when TGF-β1 and the compound of the present invention were simultaneously administered. Contrary to the Examiner's assertion that no results are disclosed for the proliferation test in Example 2, Applicant respectfully disagrees and points the Examiner to Figure 1 of the originally filed application. Figure 1 is reproduced below for the Examiner's convenience.



The graphs show the results of the proliferation test when TGF-β1 was administered without Compounds 19/24 (see white bars) and when different concentrations of TGF-β1 were

administered with Compounds 19/24 (see black bars). The graphs clearly show that the number of living cells increased when the concentration of Compounds 19/24 was increased. Thus, one of ordinary skill in the art would understand from the disclosure and guidance provided in the specification, how to make and use the presently claimed invention.

One of ordinary skill in the art would understand based on the known pharmaceutically uses of known ALK5 inhibitors, how to make and use the presently claimed invention to treat the diseases listed in Claim 15.

B. Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-11, 13-14 are rejected under 35 U.S.C. 112, second paragraph, for the following reasons:

(1) The Office Action asserts that the two rings representing "A" in Claim 1 are duplicative such that when the top structure is flipped 180°, one obtains the bottom structure and *vice versa*.

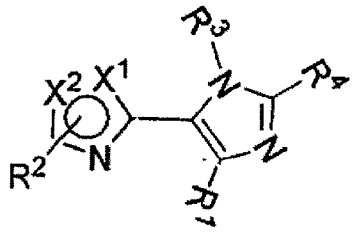
(2) The Office Action asserts that with regard to Claim 9, it is not clear what is meant by "an external medicine."

(3) The Office Action asserts that claims 7-11 are intended use claims and are duplicates of Claim 1.

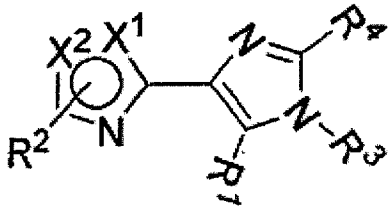
(4) The Office Action asserts that the limitation "R^1 is a phenyl with a 5 to 7 ... and benzo(1,3)dioxol" in Claims 13 and 14 are indefinite. Specifically, the Examiner states that the "bicyclic rings are not hetero atoms, are formed by condensation of 3 atoms with the phenyl not 5-7 atoms, and cannot be both hetero aromatic and non-aromatic." The Examiner suggests replacing the phraseology with "R^1 is selected from benzothiazolyl, benzoxazolyl or benzo(1,3)dioxol."

Initially, Claims 7-11 are canceled, rendering the Examiner's rejection moot.

Regarding the Examiner's first basis of rejection, Applicant respectfully traverses. The two rings represented by "A" are not duplicates of each other. Rather, two different compounds may be obtained depending on the two types of A selected. The first illustration below shows the compound which is obtained by the first A ring:



The figure below shows the compound which may be obtained by the second A ring:



Thus, as clearly shown by the illustrations, the two A rings recited in Claim 1 are not duplicates and result in two different compounds. In order to make the claims clearer, Claim 1 has been amended to show that either of the free bonds of ring A can bind to the thiazole group of the compound of Claim 1.

Applicant respectfully requests withdrawal of the rejection.

With regard to the Examiner's second basis of rejection, Applicant herewith cancels Claim 9 and adds new Claim 16 which recites that administration is "carried out by external application." Exemplary support for such an amendment may be found throughout the specification, at for example page 12, lines 22-27. Applicant respectfully requests withdrawal of the rejection.

With regard to the Examiner's third basis of rejection, as discussed above, Applicant herewith cancels claims 7-11 and adds new Claims 15 and 16, directed to a method of treating. Applicant respectfully requests withdrawal of the rejection.

Regarding the Examiner's fourth basis of rejection, Applicant herewith cancels Claim 14 and amends Claim 13 by reciting that "R^1 is selected from the group consisting of benzothiazolyl, benzoxazolyl, and benzo(1,3)dioxolyl." Applicant respectfully requests withdrawal of the rejection.

V. Rejection under 35 U.S.C. § 102(b)

Claims 10-11 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gaster et al., WO 01/62756 A1, and Bender et al., WO 02/40468 A1, individually. Specifically, the Office Action states that both references disclose compounds and compositions, which are inhibitors of ALK5.

Solely to advance prosecution, Claims 10 and 11 have been canceled, rendering the rejection moot.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The U.S. Patent and Trademark Office is hereby directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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